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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/997,464	12/23/97	STERN	D 54202/JPW/SB

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EXAMINER	
ANGELL, J	
ART UNIT	**PAPER NUMBER**
1633	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	08/997,464	STERN ET AL.	
	Examiner	Art Unit	
	Eirc Jon Angell	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on June 8, 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/997464 is acceptable and a CPA has been established. An action on the CPA follows.

Response to Amendment

2. Applicants' amendment filed on April 4, 2001 has been entered.

3. Claim 2 has been canceled.

4. Claims 1, 3-5, 11, 12 and 34-37 are pending.

5. Rejections that have not been reiterated have been withdrawn.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3-5, 11, 12, and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite for the following reasons: first, claim 1 has been amended to replace the phrase, "is transfected with DNA encoding", with "overexpresses". It is now unclear if the cells are overexpressing endogenous receptor for advanced glycation end product (RAGE) and mutant presenilin-2 protein, or if the cells require transient or stable transfection

with vector(s) comprising cDNAs encoding RAGE and/or mutant presenilin-2. Second, claim 1 step (c) recites the limitation "cell culture". There is insufficient antecedent basis for this limitation in the claim, because there is no prior recitation of "cell culture". Additionally, claim 1 step (d) recites, "comparing the level of cell death determined in step (c) with the **amount** determined..." (emphasis added). It is unclear to what the term "amount" is referring (i.e. the amount of what?). Claims 3-5, 11, 12 and 34-37 depend upon claim 1 and are therefore rejected for the same reasons.

Claim 5 is vague and indefinite because it is unclear if the cells are transiently or stably transfected with a vector comprising cDNA encoding mutant presenilin-2 or if endogenous mutant presenilin-2 protein is "overexpressed" in the cells. Furthermore, the term "overexpressed" implies that mutant presenilin-2 protein is expressed at a greater than basal level in the cells. It is unclear if there is any basal level of mutant presenilin-2 protein expression in the cells. Therefore, it is unclear how the term "overexpressed" would differ from "expressed" when used to describe the expression of mutant presenilin-2 in the cells. Any expression of mutant presenilin-2 protein could therefore be considered overexpression.

Claims 36 and 37 recite the limitation "DNA". There is insufficient antecedent basis for this limitation in the claim because there is no recitation of "DNA" in claim 1.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 11 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are referred to the guidelines on written description published January 5, 2001 in the Federal Register at Volume 66, No. 4, pp. 1099-1111 (also available at www.uspto.org).

Claim 11 is drawn to a pharmaceutical composition which comprises a compound which inhibits neurotoxicity in a cell by inhibiting interaction between receptor for advanced glycation end product (RAGE) and mutant presenilin-2 identified by the method of claim1, and a pharmaceutically acceptable carrier. The claim encompasses a genus composed of all compounds that inhibit the interaction of RAGE and mutant presenilin-2. However, the specification does not disclose a single species compound that inhibits the interaction of RAGE and mutant presenilin-2. Therefore, the disclosure is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of a compound that inhibits the interaction of RAGE and mutant presenilin-2 at the time the application was filed. Thus, the written description requirement is not satisfied for the claimed genus. Claim 12 depends upon claim 1 and is therefore rejected for the same reason.

Furthermore, the amendment filed on April 4, 2001 has been entered as requested by the applicants in the request for continued prosecution filed June 8, 2001. However, Applicants did not respond to the office action of May 10, 2001, wherein the rejection of claims 11 and 12 under 35 U.S.C. 112, first paragraph were maintained; therefore, the rejection of claims 11 and 12

under 35 U.S.C. 112, first paragraph is maintained for the reasons previously stated in the office action of May 10, 2001, a summary of which follows.

Applicants' arguments with respect to claims 11 and 12 were carefully considered but were not deemed persuasive. It was argued that the specification is enabling for providing the claimed pharmaceutical composition *in vivo* as a transgenic mouse which has been engineered with a DNA construct encoding RAGE and a mutant PS-2 can be made by routine methods and used as a model for administering the test compound (see page 19 of applicants' Response). With regard to the transgenic mouse models, it was argued that transgenic mouse models of Alzheimer's Disease were established in the art as of December, 1997, several of which express mutant forms of presenilins, or which co-express human presenilin and amyloid beta-protein precursor genes (references describing the transgenic mice have been supplied as Exhibits 6-9). Applicants' arguments have been considered but are not persuasive. While the prior art teaches transgenic mouse models engineered to display a phenotype associated with Alzheimer's Disease, as taught in the references provided in the Exhibits, and while it is known in the art to use transgenic mouse models in testing pharmaceutical compounds, claims 11 and 12 are directed to a pharmaceutical composition, not a method of testing a pharmaceutical composition. As stated in the previous Office actions, the specification does not disclose compounds encompassed by the claimed pharmaceutical compositions which inhibit neurotoxicity, and further, the state of the art at the time of filing teaches that providing a pharmaceutical composition for treating neurological disorders is neither routine nor predictable (see, e.g., page 6 of the Office action of 10/4/00, Paper No. 11, and pages 5-7 of the Office action of 1/3/00, Paper No. 9).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1, 3-5, 11, 12 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolozin *et al.* (Science, 274:1710-1713; December 6, 1996) taken with Yan *et al.* (Nature 328:685-691, 1996).

Applicant's arguments filed April 4, 2001 have been fully considered but they are not persuasive.

The claimed invention is drawn to a method of evaluating the ability of a compound to inhibit neurotoxicity and pharmaceutical compositions comprising the compounds identified by the method.

Applicants submit there is no motivation for one of ordinary skill in the art to combine Wolozin *et al.* and Yan *et al.*, and even if there was motivation, the combination does not make the claimed invention obvious. Applicants state that the only thread between the two references is that each paper characterizes a molecule which is involved in neurotoxicity or neurodegeneration in Alzheimer's disease. Wolozin *et al.* disclose overexpression of presenilin-

2 or mutant presenilin-2 in PC12 cells causes increased apoptosis induced by trophic factor withdrawal or amyloid-β (see abstract and figure 4E). Yan *et al.* disclose the isolation and characterization of a polypeptide which binds amyloid-β peptide, i.e. RAGE (see p 685, column 1). Applicants point out Wolozin *et al.* do not disclose RAGE or suggest that RAGE may interact with presenilin-2. Applicants also state the Examiner has not given a reason why one of ordinary skill in the art would have been motivated to combine these references. Additionally, it was submitted that the Examiner is using impermissible hindsight in combining the references. Also, notwithstanding the above discussion, the combination of Wolozin *et al.* and Yan *et al.* do not render obvious the claimed invention, because Wolozin *et al.* do not teach or suggest cells which overexpress mutant presenilin-2 protein. There is no hint or suggestion of Wolozin *et al.* that presenilin-1 is involved in any way with RAGE receptor proteins. Therefore, the applicants submit there is no suggestion to one of ordinary skill in the art to carry out step (a) of the claimed invention.

The Applicants state contrary to the Examiner's assertation, Wolozin *et al.* do not "disclose the claimed method" (see Office Action, page 11, last four lines). The steps of claim 1 are not disclosed. The Abstract of Wolozin, *et al.* states apoptosis induced by PS2 protein was sensitive to pertussis toxin, "suggesting that heterotrimeric GTP-binding proteins are involved." Applicants submit there is no teaching to make obvious the pharmaceutical compositions claimed.

With regards to adding the PS-2 or ALG-antisense nucleic acids to determine if the antisense nucleic acids are effective in decreasing the observed apoptotic activity, Applicants

emphasize the addition of such antisense molecules disclosed in Wolozin, *et al.* does not render obvious the claimed invention. Applicants state the Examiner is correlating the antisense molecules with the compound recited in claim 1; the cells of Wolozin *et al.* do not make obvious the cells recited in step (a) of claim 1; and that there is no recognition in Wolozin *et al.* of the existence of or significance of an interaction between RAGE and presenilin-2.

Furthermore, the Applicants submit the combination of Wolozin *et al.* and Yan *et al.* do not render obvious the pharmaceutical compositions presently claimed which comprise a compound which inhibits neurotoxicity in a cell by inhibiting interaction between RAGE and mutant presenilin-2. The interaction between RAGE and mutant PS-2 is not taught in either Wolozin *et al.* or Yan *et al.* The Applicants submit that the Examiner has used impermissible hindsight to combine these two references.

In reply, examiner maintains that there is motivation for one of ordinary skill in the art to combine Wolozin *et al.* and Yan *et al.* for the reasons stated in the previous Office Action dated October 4, 2000, a summary of which follows.

Wolozin *et al.* disclose expressing presenilin-2 or mutant presenilin-2 (e.g. N141I) in PC12 cells and treating the cells with amyloid-β results in increased apoptosis compared to untransfected controls (see figure 4). In addition, Wolozin *et al.* disclose a method comprising a) culturing the neuronally differentiated PC12 cells in the presence or absence of a compound, i.e. pertussis toxin or amyloid-β(1–42), b) determining the level of apoptosis in the control and treated cells, and c) comparing the extent of the apoptotic activity in the cells cultured in the presence of the compound compared to cells cultured in the absence of the compound to evaluate

the effect of the compound on apoptotic activity (see, e.g., page 1713, note #21). While Wolozin *et al.* does not disclose adding a nucleic acid compound to neuronally differentiated PC12 cells expressing a mutant presenilin-2 protein, or all of the claim-designated pharmaceutical carriers, Wolozin *et al.* does disclose adding PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells which do not express a mutant presenilin-2 protein. Addition of the antisense nucleic acid results in a decrease in apoptotic activity in the PC12 cell (see, e.g., page 1720, middle and right columns, Figure 1). Inasmuch as Wolozin *et al.* disclose that PC12 cells that express a mutant presenilin-2 protein have a high apoptotic activity, it would have been obvious to add PS-2 or ALG-3 antisense nucleic acids to neuronally differentiated PC12 cells expressing mutant presenilin-2 protein for the purpose of determining if the antisense nucleic acids are effective in decreasing the observed apoptotic activity in PC12 cells expressing mutant presenilin-2 protein. Moreover, adding the nucleic acids, or other compounds such as pertussis toxin or amyloid-β (1-42) to cell cultures as a pharmaceutical composition would have been obvious and well within the purview of one of ordinary skill in the art of cell culture. One of ordinary skill in the art would have been motivated to admix the compound of interest with a suitable carrier to more easily control the concentration of the compound added to the cell culture to avoid a localized high concentration of a solid compound which may be detrimental to the cells.

Wolozin *et al.* do not teach that the PC12 cells are transfected with a DNA sequence encoding RAGE and which is transfected in PC12 cells. However, Yan *et al.* teach that enhanced expression of RAGE in Alzheimer's disease, in affected neurons, in microglial and in vasculature, is consistent with the concept that amyloid-β-RAGE interaction may contribute to

neurotoxicity that results in dementia (see page 382, left column, last paragraph). Thus, it would have been obvious to one of ordinary skill in the art to provide cells associated with neurodegenerative diseases, in a method of identifying compounds which inhibit neurotoxicities associated with neurodegenerative diseases. Yan *et al.* further teach that human amyloid-β(1-40 or 1-42) purified from plaques or vascular amyloid-β from Alzheimer's disease patients inhibits binding of amyloid-β to RAGE (see, e.g., p 688, left column); that amyloid-β binding to RAGE and amyloid-β-induced cellular perturbation results in oxidant stress and cytotoxicity (see, e.g., p 688 right column, under "RAGE and amyloid-β-induced cellular stress"). Yan *et al.* indicate that RAGE can mediate amyloid-β induced oxidant stress on endothelium and neuronal cells and that the stress can be prevented by blocking access to RAGE using either anti-RAGE IgG or excess soluble receptor, and further teach that expression of RAGE increases vulnerability to amyloid-β. Yan *et al.* indicate that RAGE, if present and/or upregulated in cells important in the pathogenesis of Alzheimer's' disease, could mediate toxic effects when associated with amyloid-β. Note also that Yan *et al.* teach transfection of RAGE into COS-1 cells and the use of these transfected cells in analyzing the effect of compounds on amyloid-β activity with respect to oxidant stress (see, e.g., p 688 under "RAGE and amyloid-β-induced cellular stress).

It would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to modify the method of Wolozin *et al.* by further modifying the presenilin-2 transfected PC12 cells of Wolozin *et al.* by transfecting the cells with a vector encoding RAGE in view of the teachings of Yan *et al.* that cells transfected with RAGE are useful in studying the interaction of RAGE and amyloid-β-on oxidant stress and cytotoxicity in cells.

It is pointed out that one of ordinary skill in the art would have been motivated to provide such a modified PC12 cell to use in a method of identifying inhibitors of neurotoxic compounds, such as those associated with Alzheimer's disease, in view of the teachings of Yan *et al.* that enhanced expression of RAGE in Alzheimer's disease, in affected neurons, in microglial, and in vasculature, is consistent with the concept that amyloid-β-interaction may contribute to neurotoxicity that results in dementia. Although there was no indication in either Wolozin *et al.* or Yan *et al.* that an interaction between amyloid-β and presenilin-2 existed, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of Wolozin *et al.* that overexpression of presenilin-2 and mutant presenilin-2 protein in PC12 cells increases the cells sensitivity to amyloid-β neurotoxicity with the teachings of Yan *et al.* that overexpression of RAGE in neuronal-associated cells of increases the cells sensitivity to amyloid-β neurotoxicity for the purpose of creating cells that have a greater sensitivity to amyloid-β neurotoxicity for the purpose of identifying compounds that inhibit neurotoxicity. Applicants submit that Wolozin do teach or suggest cells which overexpress a mutant presenilin-2 protein. The cells are, however, transfected with a vector encoding mutant PS-2 protein (see, e.g., Figure 4). Cells transfected with an expression vector encoding a protein would have increased expression of the protein as compared to untransfected cells, and thus would be "overexpressing" the protein. Furthermore, if the cells were merely expressing mutant PS-2 protein, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to "overexpress" the mutant PS-2 protein in order to have an increase in the protein's effect; in this case, an increase in the cells sensitivity to amyloid-β.

With regard to Applicants submission that the addition of antisense molecules disclosed in Wolozin *et al.* do not render obvious the claimed invention because the teaching of Wolozin *et al.* do not make obvious the cells recited in step (a) of claim1 which overexpress RAGE and mutant PS-2. Wolozin *et al.* teaches that adding particular antisense molecules are effective in decreasing the observed apoptotic activity of PC12 cells expressing mutant PS-2 protein. It would have been obvious to an ordinary artisan at the time the claimed invention was made that adding the particular antisense molecules of Wolozin *et al.* to any cell expressing mutant presenilin-2 protein would decrease apoptotic activity of that cell, including the cells of the claimed invention which express mutant presenilin-2 and RAGE.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Thus, the claimed invention was obvious at the time the claimed invention was made in view of Wolozin *et al.* taken with Yan *et al.*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached on (703) 305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon Eric Angell
August 27, 2001

Anne-Marie Baker

ANNE-MARIE BAKER
PATENT EXAMINER